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EXAMINER

SOJAYA, J

ART UNIT
1655

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/027,089

App. No. 8

Portugal

Examiner

Jehanne Souaya

Art Unit

1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Feb 1, 2001

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 19-25 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 19-25 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) Notice of References Cited (PTO-892)

18) Interview Summary (PTO-413) Paper No(s). 16

16) Notice of Draftsperson's Patent Drawing Review (PTO-948)

19) Notice of Informal Patent Application (PTO-152)

17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

20) Other: _____

Art Unit: 1655

DETAILED ACTION

1. Currently, claims 19-25 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are newly applied. They constitute the complete set being presently applied to the instant Application. Prosecution for the instant application has been reopened. This action is NON-FINAL.

Priority

2. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of non-provisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. Additionally, please specify whether the parent application is a provisional application.

Art Unit: 1655

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Double Patenting

4. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

5. Claim 25 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 19 and 20 of copending Application No. 09/027,439. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Art Unit: 1655

Claim 25 is drawn to a nucleic acid probe comprising the sequence of one of SEQ ID Nos: 1-4. SEQ ID NO 1 of the instant invention is identical to SEQ ID NO 18, recited and claimed in claim 20 of the '439 application. SEQ ID NO 1 is also comprised by SEQ ID NOS 6 and 12 from the '439 application. SEQ ID NO 2 of the instant application is identical to SEQ ID NO 19, recited and claimed in claim 20 of the '439 application. SEQ ID NO 19 is also comprised by SEQ ID NO 11 from the '439 application. SEQ ID NO 3 is identical to SEQ ID NO 20, recited and claimed in claim 20 of the '439 application. SEQ ID NO 3 is also comprised by SEQ ID NO 14 from the '439 application. SEQ ID NO 4 is identical to SEQ ID NO 21, recited and claimed in claim 20 of the '439 application. SEQ ID NO 4 is also comprised by SEQ ID NO 24 of the '439 application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Art Unit: 1655

Claim 25 is drawn to a nucleic acid probe comprising the sequence of one of SEQ ID Nos: 1-4. The language “comprising” is considered open terminology and encompasses sequences with any number of nucleotides on either side of the sequence in question. Nucleic acid probes can contain hundreds of nucleotides, however it is unclear from the disclosure in the specification how many nucleotides the term “comprising” encompasses. Therefore, the recitation in the claim encompasses thousands of nucleic acid sequences for each SEQ ID NO whereas the specification has only taught a single nucleic acid sequence for each SEQ ID NO. Each of the claimed sequences is a genus for which a which a representative number of species for each genus must be disclosed to meet the written description requirement of 112, first paragraph. As set forth by the Court in *Vas Cath V. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art “with reasonable clarity” that as of the filing date applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of the species of the isolated nucleic acid sequences encompassed in claim 25, the application fails to show that applicant was, in fact, “in possession of the claimed invention” at the time the application for patent was filed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

Art Unit: 1655

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

9. Claim 25 is rejected under 35 U.S.C. 102(a) as being anticipated by Accession number

U68651.

Claim 25 is drawn to a nucleic acid probe comprising the sequence of one of SEQ ID Nos:

1-4. Accession number U68651 teaches a nucleic acid containing 521 nucleotides that comprises SEQ ID NO 3. The language “comprising” is considered open terminology and encompasses sequences with any number of nucleotides on either side of the sequence in question.

10. Claim 25 is rejected under 35 U.S.C. 102(b) as being anticipated by Cilia et al (Mol. Biol.

Evol. Vol. 13, pp 451- 461, 2/26/1996) and accession numbers X80678 and X80728.

Claim 25 is drawn to a nucleic acid probe comprising the sequence of one of SEQ ID Nos:

1-4. Accession number X80678 teaches a nucleic acid of 1459 nucleotides in length that comprises SEQ ID NO 1. Accession number X80728 teaches a nucleic acid of 1385 nucleotides in length that comprises SEQ ID NO 4. The language “comprising” is considered open

Art Unit: 1655

terminology and encompasses sequences with any number of nucleotides on either side of the sequence in question.

11. Claim 25 is provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No.09/027,439 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application 09/027,439.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 17 USPQ2d 1885 (Fed. Cir. 1991).

12. Claim 25 is rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. Claim 20 from application 09/027,439 is drawn to identically disclosed sequences in claim 25 of the instant application, however the '439 application claims 2 additional inventors than in the instant application.

Art Unit: 1655

Claim Rejections - 35 USC § 103

13. ¹⁹⁻²⁵ Claims ~~9-18~~ are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Hammond et al (US Patent 5,374,718: Dec. 20, 1994) and Hogen (US Patent 5,714,321, 102(e) date: 2/22/94) and Dyson, N.J. (Essential Molecular Biology Vol. II: A Practical Approach, chapter 5, pages 111-156, Brown, T.A. ed. Oxford University Press, Oxford, 1992) and Anderson (Gene Probes 2: Hybridization Strategy, pp 1-29, Oxford University Press, New York, 1995) in view of Cilia et al (Mol. Biol. Evol., vol. 13, pp 451-461, 1996).

The claims are drawn to a method of discriminating between or among species of Shigella an E. Coli in a sample containing organisms of one or more taxonomic groups by selecting a probe from an operon common to two or more organisms of the taxonomic groups, wherein the probe contains one or more base mismatches and wherein the probe is capable of discriminating between organisms by hybridization at two or more wash temperatures at or above the probes calculated or experimentally determined Tm, hybridizing the probe to the nucleic acid in the sample, and determining the presence or absence of hybridizing nucleic acid.

Methods of using probes to identify or differentiate closely related organisms was well known in the art at the time of the invention, as well as manipulations of reaction conditions to increase stringency, as can be exemplified by the teachings in the following references. Hammond teaches hybridization assay probes specific for chlamydia pneumoniae which can distinguish *C. pneumoniae* from its most closely related taxonomic or phylogenetic neighbors (see col. 3, lines

Art Unit: 1655

35-40). Hammond teaches obtaining suitable probes for detection and discrimination. Hammond generally teaches that all prokaryotic organisms (except for viruses) contain rRNA genes.

Hammond teaches that variable regions of rRNA sequences from the 16S rRNA of *C. pneumoniae* were identified by sequencing the rRNA of *C. pneumoniae* and its closely related phylogenetic neighbors and aligning the sequences to reveal areas of maximum homology and also alignment for regions of sequence variation (col. 3, lines 41-55). For construction of suitable probes, Hammond teaches that first, the stability of the probe:target nucleic acid should be chosen to be compatible with assay conditions, ie: hybridization involving complementary nucleic acids of higher G-C content will be stable at higher temperatures (col. 4, lines 51-65). Hammond teaches that ionic strength and incubation temperature under which a probe will be used, should be taken into account. Hammond teaches that incubation at temperatures below the optimum Tm may allow mismatched base sequences to hybridize and can therefore result in reduced specificity (col. 5, lines 8-15). Hammond further teaches that it is desirable to have probes which hybridize only under conditions of high stringency.

Hogan also teaches a method for preparing probes for use in qualitative and quantitative assays wherein the probes are capable of detecting and differentiating between eubacteria (see abstract). Hogan also teaches the hybridization of *E. Coli* probes to closely related organisms such as *Shigella boydii*, *Sh. flexneri*, *Sh. dysenteriae*, and *Sh. sonnei* (see col. 52, table 54). Hogan also generally teaches hybridization strategies, including variations in temperature, probe length, probe composition, and ionic strength in methods of identification of target nucleic acids

Art Unit: 1655

(cols 7-11) and specifically points out that use of temperatures below the optimum (Tm) may allow mismatched base sequences to hybridize and can therefore result in reduced specificity (col. 10, lines 21-24). Hogan also specifically teaches using filter hybridization methods, and the use of rRNA sequences in distinguishing between eubacteria (cols 1 and 2).

Anderson teaches hybridization strategies in constructing probes for methods of screening and identification. Anderson teaches factors affecting the rate of hybridization and the stability of hybrids, (p. 3-13) including probe length, composition, and temperature. Anderson specifically applies these manipulations to filter hybridization. Anderson also specifically teaches that to detect closely related family members, it is better to use stringent hybridization conditions followed by stringent washing conditions (for example, from the teaching of the previous three references, the ordinary artisan would be taught that such a condition could involve high temperature, etc) (p. 13, last sentence).

Dyson teaches that nucleic acid hybridization is an important component of many molecular biology techniques, and that specifically, filter hybridization methods exploit the specificity of molecular hybridization for the detection of rare sequences in a complex mixture (see p. 111, first paragraph). Dyson teaches different methods for immobilization of nucleic acids on filters (pp 111-132) and teaches factors affecting hybridization of nucleic acids (pp 132-151). Dyson teaches that such factors include Tm, base composition, mismatching (p 133), and ionic strength affect hybridization. Dyson teaches that filter hybridization involves three basic steps: pre-hybridization, hybridization, and washing (p. 137, section 3.4). Dyson teaches that after

Art Unit: 1655

hybridization, the filter is washed to remove the probe. Dyson teaches that short DNA duplexes have a reduced melting temperature and the Tm of oligonucleotide probes can be calculated, although the actual Tm should be determined experimentally (see p 146). Dyson specifically teaches that oligonucleotides are hybridized at a temperature between 5 and 10 degrees below the Tm for 14-48 hours and that filters are then washed four times *at* the hybridization temperature (see p. 147, lines 1-3). Dyson teaches that often, such a wash is enough, however Dyson teaches that if the filters still show considerable activity above background, the wash temperature should be increased by 2-3 °C and the wash should be repeated.

Although neither Hammond, Hogan, Dyson or Anderson teach using the probes of the instant invention, Cilia et al teaches sequence heterogeneities among 16S RNA sequences of *E. Coli* and *Shigella* (see abstract, and figure 3) and teaches nucleotide differences among Eubacteria by showing a line up of regions from 16S genes across species levels, showing the nucleotide sequence similarities and differences. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct the DNA sequences of the claimed invention for the use of probes and primers that could distinguish *Shigella* from *E. Coli*. Methods of distinguishing between different eubacteria using probes and primers that target regions of similarity and differences were readily known in the art at the time of the invention and is exemplified by the Hogan patent. The ordinary artisan would have been motivated to construct probes and primers of the claimed invention to identify and differentiate *E. coli* from *Shigella* as Cilia teaches how closely related the two genus of bacteria are (see Fig 1). Cilia et al also teaches

Art Unit: 1655

the sequences of SEQ ID NOS 1, and. [Applicant was faxed a copy of the results of a sequence search, which also discloses variants of SEQ ID NO 2, and the complete nucleotide sequence of SEQ ID NOS 1 and 4. This sequence search cites Cilia et al, identified above, as disclosing the accession numbers for these results (see table 1 of Cilia et al).] As the sequences of the 16S rRNA and rDNA sequences of the *Shigella* species and *E.coli* sequences were known at the time of the invention, it would have been obvious for the ordinary artisan to construct probes and primers to regions of variability to be able to differentiate the closely related bacteria. Such methods were readily known in the art as is shown by the large amount of literature available in the art that identifies regions of variability among closely related bacteria for the purpose of constructing probes and primers useful in methods of differentiation.

It would have further been *prima facie* obvious to one of ordinary skill in the art to raise the temperature of the wash step to achieve maximum specificity and selectivity as Dyson teaches that the temperature of the wash step can be varied by incrementally increasing the temperature. Dyson also provides examples of lengths of probes as well as suggested hybridization and wash temperatures (see table 2, p. 147). In each case, the wash temperature is above the hybridization temperature. Therefore, although Anderson and Dyson teach hybridizing 5-10 degrees *below* the T_m of the probe, Dyson teaches washing above the hybridization temperature and that the wash temperature can be increased by 2-3 degrees. With such a teaching, and the examples in table 2, it would have been readily apparent to one of ordinary skill in the art to increase wash temperatures by 2-3 degrees at a time, and repeat as needed until suitable hybridization had occurred. It would

Art Unit: 1655

have further been *prima facie* obvious to one of ordinary skill that because Dyson teaches *suggested* conditions and teaches that manipulations of conditions, such as wash temperature, can be performed to achieve the desired result, a certain amount of manipulation of conditions (such as changing salt concentration, varying temp of both hybridization and washing steps) could be necessary. As the level of skill in the art regarding hybridization of oligonucleotides is very high, the ordinary artisan would have considered that the identification of optimum Tm for washing is a matter of routine optimization and that while one would initially wash at Tm below the Tm of the probe, where such conditions are insufficient to distinguish, the ordinary artisan would know to adjust the conditions, either by increasing the temperature or adjust the buffer (ie: salt concentration).

Response to Arguments

Applicant traverses that the publication of the Sabat et al reference proves that the new claims are unobvious. Applicant further traverses that the conclusion of Sabat “ to the best of our knowledge, this is the first report of a PCR protocol based on amplification of 16S rRNA that affectively distinguishes E. Coli for these closely related bacteria” (p 849, para 2) provides the clear and inescapable conclusion that hybridization protocols could not, at the time the application was filed, be used to discriminate between and among Shigella and E. Coli species and that therefore the claims cannot be obvious over the prior art. This argument has been thoroughly reviewed but was found unpersuasive because the criteria for determining whether an invention

Art Unit: 1655

overcomes the requirements of 35 USC 103 is different from the requirements needed to publish a scientific paper. Furthermore, the assertion of Sabat that ' this is the first report... of the amplification of 16S rRNA that effectively distinguishes between E. Coli and [Shigella}' would apply to a rejection based on 35 USC 102, as to the novelty of the invention. The examiner does not disagree that the art is lacking in a teaching that specifically distinguishes E.coli from Shigella, however the examiner has not rejected claims 19-24 under 35 USC 102, but under 35 USC 103. The rejection outlined above, shows that methods of manipulating wash temperatures would have been obvious to one of ordinary skill given the teaching of Dyson.

Applicant further traverses that prior methods have failed to distinguish between and among E. Coli and shigella, this argument has been thoroughly reviewed but was found unpersuasive because the sequences used by Hogan were different than those used by applicant. The office action maintains that while prior art methods do not specifically teach distinguishing between and among E.coli and Shigella, manipulating a probe nucleotide sequence as well as the parameters of hybridization reactions were well within the skill of the ordinary artisan at the time of the invention. Furthermore, the ordinary artisan would have been motivated to distinguish between such closely related bacteria as the prior art repeatedly teaches the need to do so.

Applicants traversal that the cited references fail to show that the claimed invention was obvious is considered moot as the rejection has been newly applied. However, the examiner notes that applicant has dissected the previously made rejection and attacked each reference individually. In response to applicant's arguments against the references individually, one cannot

Art Unit: 1655

show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

14. No claims as written are allowable over the prior art, although allowable subject matter does exist. As the examiner attempted to point out with the citation of a number of references that teach target nucleic acid (from closely related taxonomic groups using hybridization of probes to variable regions) identification and probe hybridization condition manipulations, the level of skill in the art at the time of the invention was extremely high, and routine manipulations of hybridization and washing conditions was well within the skill of the ordinary artisan. Furthermore, the art provides motivation for the artisan to manipulate conditions to achieve conditions of as high specificity and stringency as possible, see Dyson. Applicant's specification, however, teaches that some results are unexpected. Thus while applicant's general method is obvious (ie: claims 19-25), certain results are unexpected. Applicant asserts in the response that the findings of Sabat prove that the instant invention is independent of sequence and the process for discriminating. The examiner maintains, however, that the method taught in the instant application cannot be generally applied, that the results are unexpected, and that such results are dependent on sequence. See for example p. 12, Example 1 in the specification. The specification teaches that the probe was designed from the 71-100 nucleotide position of the rrn operon 16S

Art Unit: 1655

subsequence of *S. boydii*. The specification also teaches, however, that at 66 °C, all the organisms were identified by such a probe (SEQ ID NO 1) and that at 72 °C, only *S. Sonnei* and *E. coli* were identified by the probe. Similar unexpected results were observed for each of the other 3 probes taught in the specification. That is, none of the probes actually identified the organism they were designed for. Thus this shows that the results were both dependent on the sequence of the probe and the conditions used for the hybridization reaction. Claims directed to such unexpected results would be allowable over the prior art. The exact method steps outlined in the flow chart, including the specific sequences at each step of the method, are also allowable, because such steps, in the order used, gave unexpected results (sequences that were thought to hybridize with one organism, actually discriminated a different organism, which was unexpected).

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner

Jehanne Souaya
April 10, 2001


W. Gary Jones
Supervisory Patent Examiner
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